

### **REMARKS**

Claims 1-4, 6-31, and 35-41 are pending in the instant application. The Examiner has rejected all of the pending claims under 35 U.S.C. §103 and under the judicially created doctrine of obviousness-type double patenting.

#### **Objection to the Specification**

The Examiner maintains that the amendment filed on February 18, 1997 introduces new matter into the specification, and therefore objects to the specification under 35 U.S.C. §132. According to the Examiner, the boxes which were blank in the specification are now stippled in two different ways, cross hatched or blank. Allegedly, the stippling in the figures and in the specification do not match, and the crosshatch pattern in the figure is in the opposite direction of that in the specification. Therefore, the Examiner says that it is unclear which sequences are intended to be linked. Moreover, the Examiner states that even if the figure were of higher quality and one could clearly match the various shaded boxes with the portions of the figure, the figure lacks sufficient information to verify which box in the specification should be filled with which shading. In response to this objection, Applicants hereby agree to cancel the substitute page 10 so that original page 10 of the specification remains.

#### **Rejection under the judicially created doctrine of obviousness type double patenting**

The Examiner provisionally rejects claims 1-4, 6-8, 38 and 39 under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of copending U.S. Serial No. 08/486,858. Claims 38 and 39 refer to particular vectors on deposit with the ATCC whose particular structure is not obvious over claims 1-3 of U.S. Serial No. 08/486,858. Applicants do not acquiesce that this provisional rejection is proper as to the other claims. Applicants will take appropriate steps to prevent double patenting if an actual rejection is made upon notification of allowable subject matter.

### Rejection under 35 U.S.C. §103

The Examiner continues to reject the pending claims as obvious over Temin in combination with several other references including Bender *et al.* and Cone *et al.* Applicants have repeatedly explained some of the reasons why the presently claimed invention is patentable over these references. Applicants have explained that the present invention allows the transduction of mammalian cells without selection. The Examiner has cited the Cone *et al.* reference for the teaching that transduction could be performed without a selection step prior to the instant invention. In support of the patentability of the present invention, Applicants submitted the Declaration of Dr. Lawrence Cohen as executed on October 11, 1996 (a copy is enclosed herewith). Therein, the Declarant states that it is his expert opinion that the concentrations of retrovirus disclosed by Cone *et al.* would not have provided one of ordinary skill in the art with a reasonable expectation of successfully transducing mammalian cells without selection. Dr. Cohen supports this fact with personal statements and with a reference which shows that one must generally use a concentration of retrovirus that is at least about an order of magnitude higher than that taught by Cone *et al.* in order to practice efficient transduction without selection.

#### *(1) Regarding the particular vectors described by ATCC deposit numbers*

Applicants added claims 38-41 by way of an amendment filed on February 18, 1997. These claims describe particular ATCC deposited vectors, namely ATCC 68,754, ATCC 68,755, and mutants thereof which contain the B2 mutation.

The Examiner has rejected claims 38 and 39 directed to the deposited vectors as unpatentable over Temin in view of Bender *et al.* and Cone *et al.* First, these claims are patentable as are the others discussed, *infra*, because there is no teaching or suggestion of vectors which lack a functional selectable marker as Applicants have explained in other responses. However, these claims 38 and 39 are also patentable because there is no teaching or suggestion of vectors having the particular characteristics of these specific vectors in the references alone or in combination.

The Examiner will note detailed description of the MFG vector, ATCC deposit number 68,754 at Figure 2c and Figure 3 among many other places in the specification. Likewise, detailed description of  $\alpha$ -SGC, ATCC deposit number 68,755 is provided at Figure 4 among other places in the specification. There is no teaching or suggestion in any of the references cited of vectors having these particular characteristics.

The Examiner has rejected claims 40 and 41 directed to the aforementioned ATCC deposits comprising B2 mutation over Temin in view of Cone et al., Anderson and deVilliers taken with either Hilberg *et al.* or Holland *et al.* and further in view of either Franz *et al.* or Weiher *et al.* First of all, since none of the prior art teaches or suggests vectors which lack a functional selectable marker, these claims are patentable for this reason alone. However, the vectors of claims 40 and 41 are also patentable because there is certainly no teaching or suggestion in the prior art of these particular ATCC deposited vectors and B2 mutants thereof. Hence, these claims are patentable for this additional reason as well.

(2) *Cone et al. is not enabling*

It is a fundamental principle of the patent law that a reference must be enabling in order to be used to defeat patentability. Stated differently, for a rejection under §103 to be proper, the combined references must produce the invention as claimed. Applicants have shown that this is not the case with the references cited by the Examiner. Applicants have provided corroborating evidence in the form of an expert's declaration. The Examiner states that this Declaration has been given some weight, but that the statements of Dr. Cohen are not dispositive of the issue of obviousness because of the lack of factual evidence of the non-enabling disclosure of Cone et al. Applicants submit that the Examiner is not giving the statements of Dr. Cohen the legally proper weight. The courts have repeatedly indicated that one well qualified in the highly technical art of the claimed invention is entitled to express his expert opinion and that opinion is entitled to be given consideration

with other evidence in determining whether the conclusion of obviousness is supported by the opinion of the Examiner as to what the prior art teaches. *In re Fay et al.*, 347 F.2d 597, 146 USPQ 47 (CCPA 1965), *In re Carroll*, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979). Moreover, the courts have stated that if an affidavit provides evidence to support the legal conclusion of unobviousness, it must be considered, including the statement of opinion by the expert. *In re Cotner*, 347 F.2d 582, 146 USPQ 55 (CCPA 1965), *In re Lindell*, 385 F.2d 453, 155 USPQ 521 (CCPA 1967), *In re Metcalf et al.*, 394 F.2d 558, 157 USPQ 423 (CCPA 1968).

(3) *The instant invention is patentably distinct from the prior art cited by the Examiner*

Temin *et al.* do not teach or suggest several aspects of the presently claimed invention. First of all, Temin *et al.* teach constructs which require the use of a selectable marker. Secondly, the present invention uses a helper-free retroviral system which differs from that taught by Temin *et al.* in that Temin *et al.* require helper virus for viral propagation.

Bender *et al.* teach the mechanism of high virus titer production from retroviral packaging cell lines in which retroviral vectors containing a selectable marker either coding for neomycin (neo) or hygromycin B (hph) phosphotransferase gene (See Fig. 1 for the retrovirus vector constructs) are employed for virus titer production. The inclusion of a dominant selectable marker in the genome of the retroviral vectors makes the *in vivo* gene therapy less practicable due to the undesirable co-expression of this antibiotic resistant gene product in tested animals. In contrast, the present invention uses retroviral vectors that are capable of producing high virus titer without a selectable marker and are suitable as retroviral vectors for *in vivo* gene therapy. Bender *et al.* do not teach or suggest the possibility of using marker-free retroviral vectors.

Regarding Cone *et al.*, Applicants have demonstrated by the declaration of Dr. Cohen that the teachings are not enabling. Applicants request the Examiner to

consider the very reference itself at this time as further evidence of that fact. At page 6352, in the sentence bridging columns 1-2, Cone *et al.* state that "...many of the vectors constructed in our laboratory....depend on the production of a spliced transcript for expression of a selectable gene such as neo..." Moreover, the only passage in the reference which suggests that transduction without a selectable marker might be possible is unsupported by data. Cone *et al.* merely generically state without support that "one can readily isolate lines such as  $\psi$ -AM2275 that produce  $>10^5$  recombinant virus per ml. These titers are high enough to facilitate the nonselective introduction of genes into 100% of a population of cells at high enough cell numbers to allow rapid analysis of DNA, RNA or protein" (page 6353, column 1, paragraph 2). There is absolutely no corroborating evidence or data to support such a statement.

(4) *The Examiner has not set forth a proper prima facie case of obviousness*

The caselaw is clear that in order for references to be combined to produce a rejection under §103, it must be obvious that their teachings can be combined. *In re Avery*, 518 F.2d 1228, 186 USPQ 161 (CCPA 1975). Obviousness cannot be established by combining the teachings the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276. When the incentive to combine the teachings of the references is not immediately apparent, it is the duty of the Examiner to explain why the combination of the teachings is proper. *Ex parte Skinner*, 2 USPQ2d 1788 (Bd. Pat. App. and Int. 1986).

With respect to the rejection of claims 1-4, 6-8, 20, 21 and 35-39 over Temin in view of Cone *et al.*, Applicants submit that even if the references are combined, the claimed invention is not produced since as noted above, Cone *et al.* do not teach transduction without a selectable marker. With respect to the rejections of claims involving Bender *et al.*, there is no teaching or suggestion that including part of a gag sequence results in the ability to eliminate the selectable marker. Hence, it is no

more than hindsight for the Examiner to combine these three references in a rejection under §103. With respect to the additional rejections for which such references as Kenten *et al.*, Kuo *et al.*, Emerman *et al.*, Yee *et al.*, Yu *et al.*, Anderson, de Villiers, Hilberg *et al.* or Holland *et al.* are cited as allegedly disclosing particular aspects of some embodiments of the invention described by dependent claims, Applicants submit that these rejections are now obviated. That is, none of these secondary or tertiary references suggest combining the features which they allegedly teach or suggest with a retroviral of the present invention which does not contain a selectable marker.

*(5) The present invention provides unexpectedly superior results over the vectors of the prior art*

The patent law has long recognized that unexpected results can serve as strong evidence of the nonobviousness and hence as evidence of the patentability of an invention. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The retroviral vectors according to the present invention possess unique configuration. It is this unique configuration including a splice donor and splice acceptor site and a partial gag sequence which produces the high transduction frequencies of these vectors. This in turn allows for transduction without the use of a selection step. In turn, because a selection step is not required, cells transduced by these vectors may be placed *in vivo* without the delay of a selection step. This represents an unexpectedly superior result over prior art retroviral vectors.

CONCLUSION

Applicants submit that the presently-pending claims are now in condition for allowance. If any issues arise which may be resolved by way of a telephonic interview, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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